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<b>(54) Title:</b> SYNTHETIC PROTEINS AS IMPLANTABLES  <b>(57) Abstract</b>  Copolymers are provided having varying ratios of elastin and fibroin repeating units. By varying the length of segments of the elastin and fibroin repeating units, the absorption can be greatly varied. Tensile strengths remain relatively constant regardless of the composition within the prescribed ranges. The copolymer compositions and recombinant fibroin can be used for the production of a wide variety of formed objects and amorphous masses for use as implants.		

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## SYNTHETIC PROTEINS AS IMPLANTABLES

### INTRODUCTION

#### 5 Technical Field

The field of this invention is the production and use of bioresorbable polypeptide polymers.

#### Background

10 The rate at which an implanted material resorbs or biodegrades within the body can be a major factor in determining its utility as a biomaterial. So called inert materials, such as metals, ceramics and plastics have been shown to be useful for permanent implants. However, in  
15 applications in which a device serves as an aid to healing or as a temporary aid in surgical repair, a resorbable material has the advantage of not having to be removed, once healing has occurred. Resorbable sutures and staples, bone pins and screws, wound dressings, and injectable drug  
20 delivery systems or depots are examples of such devices. There are very few materials available today which have the physical, chemical and biological properties necessary for the fabrication of medical devices, which must degrade and resorb in the body without detrimental consequences.

25 Various synthetic organic polymers have found use, such as polylactides, polyglycolides, polyanhydrides and polyorthoesters, which degrade in the body by hydrolysis. Collagen, glycosaminoglycans and hyaluronic acid are examples of natural implantable materials which resorb at  
30 least partially by enzymatic degradation. The rates of

resorption are limited to the nature of the particular material and modifications can change the rate of resorption, but at the same time may adversely affect the desired properties of the product.

5 Illustrative of efforts to vary resorption characteristics by compositional changes are synthetic resorbable sutures composed of copolymers of lactide and glycolide. By varying the ratio of lactic acid to glycolic acid, the rate of resorption may be varied. Unfortunately,  
10 rapidly resorbing compositions tend to be soft and weak. Slow resorbing compositions are stiff and strong. However, their resorption, which is hydrolytic, produces acid buffered by the tissue medium, where erosion occurs at the polymer surface. In addition, however, hydrolysis may occur  
15 internally, where the resulting acid catalyzes and accelerates the degradation of the polymer. Thus, internal pockets of degradation can lead to rapid and catastrophic failure of mechanical properties.

There is, therefore, a need for products which can be  
20 used in the production of implantable devices. Such products should have the desired mechanical properties of tensile strength, elasticity, formability, and the like, provide for controlled resorption, and be physiologically acceptable.

25

#### Relevant Literature

U.S. Patent No. 5,243,038 describes the preparation of high molecular weight, protein polymers and copolymers comprising long segments of small repeating units.  
30 Bioactive Polymeric Systems, Gebelein, C. G. and Carraher, C. E., eds., Plenum Press, New York, 1985; Contemporary Biomaterials, Boretos, John W. and Eden, Murray, eds., Noyes Publications, New Jersey, 1984; and Concise Guide to Biomedical Polymers: Their Design, Fabrication and Molding,  
35 Boretos, John W., Thomas pub., Illinois, 1973, describe compositions, characteristics, and applications of biomaterials.

### SUMMARY OF THE INVENTION

Protein copolymers are provided having segments varying in the number of repetitive units, based on fibroin and elastin. The protein copolymers and silk homopolymers find  
5 use in the production of a wide variety of implantable devices and components thereof.

### DESCRIPTION OF SPECIFIC EMBODIMENTS

Implantable devices and components thereof are provided  
10 comprised of recombinant novel copolymers having alternating segments of repetitive units based on fibroin (silk) in combination with elastin or recombinant polymers of fibroin. Particularly, the units for the most part are GAGAGS (SEQ ID NO:01) and VPGVG (SEQ ID NO:02), respectively, although some  
15 variations are permitted, such as the particular order of the amino acids in the sequence and conservative substitutions, such as, but not limited to, replacing serine with threonine and glycine with alanine.

In the copolymers, by varying the ratio of the two  
20 different units, the length of the segments comprising each of the units, the molecular weight, any intervening sequences, modifications to the individual repeating units, and the like, one can vary the tensile properties of the product only moderately, such as elasticity, stiffness,  
25 hardness, ease of processing, and flexibility, while one can substantially vary the rate of resorption. Faster resorption can be achieved by reducing the number of repeating units of silk in the silk segment below about 8 units or increasing the number of elastin units per elastin  
30 segment to greater than 8, individually or in combination.

For the copolymers, the ratio of the average number of elastin units to the average number of silk units per segment of the repetitive units will be in the range of about 0.5, usually about 1-5. For the most part, there will  
35 be at least two fibroin units per segment and not more than about 12, usually not more than about ten, preferably ranging from about 2-8. For the elastin units, there will

usually be at least two, more usually at least about four, generally ranging from about 6-32, more usually from about 6-18, preferably from about 6-16. The percent of amino acids contributed by the silk units will generally range  
5 from about 15-65%, more usually from about 15-60%, preferably about 20-55%.

The copolymers which find use in the invention will generally range from about 15-80% of amino acids provided by fibroin units, where the average number of elastin to silk  
10 units will range from about 0 to 8.

The polymers will be at least about 15 kDa and generally not more than about 150 kDa, usually not more than about 125 kDa, preferably ranging from about 35-100 kDa. In order to achieve the copolymers, the number of segments will  
15 provide for the desired molecular weight. Therefore, the number of segments can vary widely, depending upon the size of each individual segment. Thus, the number of segments may vary from about 2-40, more usually ranging from about 6-20.

Based on the method of preparation, there may be non-repetitive units at the N- and C- termini. Usually, the terminal sequences will contribute fewer than ten number percent of the amino acids, more usually fewer than five number percent of the amino acids. Generally, the sequence  
20 will range from about 0-125 amino acids, more usually from about 0-60 amino acids, where the total number of amino acids will generally not exceed about 100 amino acids, more usually not exceed about 50 amino acids.  
25

For special applications the polymers may be modified by  
30 introducing intervening sequences between segments or blocks of segments, where the total number of repeating units per block may vary from about 4 to 40, thus involving two or more segments. The intervening sequences may include from about 1 to 60, usually about 3 to 40 amino acids, and may  
35 provide for a wide variety of properties. For example, by including amino acids which have chemically reactive sidechains, one may provide for sites for linking a variety

of chemically or physiologically active compounds, for cross-linking, for covalently bonding compound which may change the rate of resorption, tensile properties or the like. Thus amino acids, such as cysteine, aspartic acid, glutamic acid, lysine and arginine may be incorporated in these intervening sequences. Alternatively, the sequence may provide for sequences which have physiological activity, such as cell binding, specific protein binding, enzyme substrates, specific receptor binding, and the like. In this manner, the useful properties of the basic protein may be greatly varied in accordance with the intended use, being tailored for specific applications.

The polymers have good mechanical properties to form a wide variety of products. The protein polymers may be drawn, molded, cast, spun, extruded, or the like, in accordance with known ways for forming structures such as films, formed objects, fibers, or unformed structures, such as amorphous masses, and the like. Also, gels may be formed which may be shaped in a variety of ways, depending upon the particular application. The compositions can be sterilized by conventional ways to provide sterile products.

The subject compositions can be used to provide a wide variety of devices, such as membranes, sutures, staples, bone pins, screws, wound dressings, and as drug depots, where the products may be formed prior to implantation or *in situ*. The compositions as formed are found to provide the necessary mechanical properties for the particular applications, the resorption times can be controlled so as to ensure mechanical maintenance during the time required for structure integrity, and at the same time ensuring that the device or material need not be manually removed, since the material undergoes resorption.

The subject compositions may be used in combination with other materials, such as collagen, fibrinogen, and other natural proteins; hyaluronic acid, dextran, or other polysaccharides; or polyethylene oxide, polyhydroxyalkanoates, or other polyesters, to produce

blended materials to provide a larger range of physical and biological properties, for applications, such as wound dressings or membranes for the prevention of surgical adhesions. For example, the protein polymer SELP3 combined  
5 with sodium hyaluronate, in equal proportions by weight, may be used to prepare a film, which compared to pure hyaluronate gels, exhibits greater mechanical toughness and a decreased resorption rate.

The compositions may be prepared in accordance with the  
10 manner described in U.S. Patent No. 5,243,038. This procedure involves synthesizing small segments of single stranded DNA of from about 15-150 nucleotides to provide a plurality of fragments which have cohesive ends, which may be ligated together to form a segment or a plurality of  
15 segments. The first dsDNA fragment is cloned to ensure the appropriate sequence, followed by the addition of successive fragments, which are in turn cloned and characterized, to ensure that the integrity of the sequence is retained. The fragments are joined together to form a "monomer" which then  
20 becomes the major repeating building block of the polymer gene.

Alternatively, long single strands may be prepared, cloned and characterized, generally being of at least 100 nucleotides and up to about 300 nucleotides, where the two  
25 single strands are hybridized, cloned and characterized and may then serve as the monomer or the building block. The monomers may then be multimerized, having complementary termini, particularly cohesive ends, so that the polymers will have two or more monomers present. The multimers may  
30 then be cloned in an appropriate vector and characterized to determine the number of monomers and the desired size polymer selected. Expression can be achieved in an expression host using transcriptional regulatory regions functional in the expression host. The expression host can  
35 be prokaryotic or eukaryotic, particularly bacterial, e.g. *E. coli*, *B. subtilis*, etc.; yeast, e.g. *Saccharomyces*, *Neurospora*, etc.; insect cells, plant cells, and the like.



If desired, a signal sequence may be provided for secretion of the polymer. A wide variety of signal sequences are known and have been used extensively for secreting proteins which are not normally secreted by the expression host.

5 After completion of expression, where the protein is retained in the host, the cells are disrupted and the product extracted from the lysate. Where the product is secreted, the product may be isolated from the supernatant. In either case, various techniques for purifying the  
10 products may be employed, depending upon whether the products are soluble or insoluble in the medium. Where insoluble, impurities may be extracted from the polymer, leaving the polymer intact. Where soluble, the polymer may be purified in accordance with conventional ways, such as  
15 extraction, chromatography, or the like.

The following examples are offered by way of illustration and not by limitation.

#### EXPERIMENTAL

20 Example 1. Preparation of polymers.

E. coli strain EC3 containing the respective plasmid encoding each polymer shown in Table 1 below, was prepared in accordance with the methods described in U.S. Patent No. 5,243,038. Each strain was then fermented using a fed-  
25 batch method.

Biomass for each polymer was harvested from the fermentation broth by centrifugation in a Sorval RC3B using a H6000A rotor at 5,000 rpm for 30 minutes at 10°C to yield a packed cell paste. 500 grams of cell paste was  
30 resuspended in 2 liters of 50 mM Tris buffer (pH=8.0). The cell slurry was homogenized using a Manton Gaulin cell disrupter at 7-8,000 psi with three complete passes of the liquid. The cell homogenate was passed through a chilled heat exchanger to maintain the temperature at 15°C or less.  
35 Pancreatic DNase was added to the homogenate to a final concentration of 1 µg/ml and stirred at room temperature for 2 hours. The homogenate was centrifuged in a Sorval RC3B

centrifuge using a H6000A rotor at 5,000 rpm for 1 hour at 10°C.

For SELP0, 3, 7, and 8, the supernatant was placed into 12-14,000 molecular weight cut-off dialysis bags and dialyzed against 2 changes of 100x volume of 20 mM sodium acetate buffer (pH=4.7) for 24 hours. The contents of the bags were transferred to centrifuge bottles and centrifuged in a Sorval RC3B centrifuge using a H6000A rotor at 5,000 rpm for 1 hour at 10°C. The supernatant was removed to a large beaker and the pH adjusted to 8.0 by addition of 30% ammonium hydroxide. Saturated ammonium sulfate was then added to reach a final concentration of 20% for SELP0, 25% for SELP8 and 3, and 33% for SELP7. The solution was stirred at room temperature for 1 hour. The solution was centrifuged in a Sorval RC3B using a H6000A rotor at 5,000 rpm for 30 minutes at 10°C. The pellet was resuspended in 2 liters of deionized water, placed in dialysis bags, and dialyzed against 3 changes of deionized water of 100x volume over 48 hours. The contents of the bags were shell frozen and lyophilized to dryness.

For SELP4 and 5, the centrifuged homogenate supernatant was directly precipitated with ammonium sulfate at a concentration of 25%. The solution was then centrifuged in a Sorval RC3B using a H6000A rotor at 5,000 rpm for 1 hour at 10°C. The pellet was resuspended in 5 liters of 4M LiBr and stirred at 4°C for 16 hours. The solution was centrifuged in a Sorval RC3B centrifuge using a H6000A rotor at 5,000 rpm at 10°C for 1 hour. The pH of the supernatant was adjusted to pH 3.7 by slow addition of 1M acetic acid at 4°C. The solution was centrifuged in a Sorval RC3B using a H6000A rotor at 5,000 rpm at 10°C for 1 hour. The supernatant pH was adjusted to 8.0 by addition of ammonium hydroxide and then dialyzed against 3 changes of 100x volume deionized water over 48 hours. The solution was removed from dialysis and centrifuged in a Sorval RC3B using a H6000A rotor at 5,000 rpm at 10°C for 1 hour. Saturated ammonium sulfate was added to the supernatant to reach 25%

of saturation and stirred for 1 hour. The solution was centrifuged in a Sorval RC3B using a H6000A rotor at 5,000 rpm at 10°C for 1 hour. The pellet was dissolved in 4.5M LiBr, placed in dialysis bags, and dialyzed against 3 changes of 100x volume of deionized water. The contents of the bags were shell frozen and lyophilized to dryness.

All reagent solutions used in the following procedures were depyrogenated prior to use by filtration through a 10,000 nominal molecular weight cut-off hollow fiber cartridge (AG Technologies). All glassware and utensils used were sterilized and depyrogenated by heating at 180°C for 4 hours. 4-5 grams of all SELP dried polymers were dissolved in 1.2 liters of 10M urea. 20 mls of 2M Tris pH8.0 and 780 mls of milli-Q water were added. The solution was sonicated to promote full dissolution of the protein. 500 grams of Whatman DE52 ion exchange resin was prepared by precycling through acid and base treatment as recommended by manufacturer prior to and in between each usage. The resin was finally equilibrated with 6M urea, 20 mM Tris pH8.0 in a beaker with gentle stirring. The resin was filtered in a buchner funnel until excessive liquid was removed. The cake of resin was placed in a beaker and the protein solution was added. The slurry was stirred gently for 1 hour. The slurry was filtered in a buchner funnel and the liquid was collected in a cleaned vacuum flask. 500 grams of fresh precycled and equilibrated resin was added to a clean beaker and the filtered solution was added. The slurry was stirred gently for 1 hour and filtered again. The filtered solution was once more combined with 500 grams of freshly precycled and equilibrated resin, stirred for 1 hour, and filtered. The final filtered solution was placed in 6,000 molecular weight cut-off dialysis bags which had been soaked in 0.5N NaOH for at least 24 hours. The solution was dialyzed against 3 changes of 100x volume of deionized water. The dialyzed solution was removed from the bags, placed in depyrogenated lyophilization flasks and lyophilized to

dryness. Employing the above procedure, the following polymers were prepared.

TABLE 1

5	Polymer (MW)	Polymer Block Sequence <sup>1</sup>	Domain Abbr. <sup>2</sup>	E/S <sup>3</sup>	%S <sup>4</sup>
	SELP0 (80,502)	[(VPGVG) <sub>8</sub> (GAGAGS) <sub>2</sub> ] <sub>18</sub> (SEQ ID NO:03)	E8S2	4.0	21.9
	SELP8 (69,934)	[(VPGVG) <sub>8</sub> (GAGAGS) <sub>4</sub> ] <sub>13</sub> SEQ ID NO:04)	E8S4	2.0	35.3
	SELP7 (80,338)	[(VPGVG) <sub>8</sub> (GAGAGS) <sub>4</sub> ] <sub>13</sub> (SEQ ID NO:05)	E8S6	1.33	45.0
	SELP3 (84,267)	[(VPGVG) <sub>8</sub> (GAGAGS) <sub>4</sub> ] <sub>12</sub> (SEQ ID NO:06)	E8S8	1.0	51.9
10	SELP4 (79,574)	[(VPGVG) <sub>12</sub> (GAGAGS) <sub>8</sub> ] <sub>9</sub> (SEQ ID NO:07)	E12S8	1.5	42.2
	SELP5 (84,557)	[(VPGVG) <sub>16</sub> (GAGAGS) <sub>8</sub> ] <sub>6</sub> (SEQ ID NO:08)	E16S8	2.0	35.7

<sup>1</sup> The first and last block domain of each polymer is split within the silk blocks such that both parts sum to a whole domain. All polymers also contain an additional head and tail sequence which constitutes approximately 6% of the total amino acids.

<sup>2</sup> Designates the number of consecutive blocks per repeating domain (E = elastin-like block, S = silk-like block)

<sup>3</sup> Ratio of blocks per polymer.

<sup>4</sup> % of total amino acids in polymer contributed by silk-like blocks.

Other polymers which were prepared include [(VPGVG)<sub>32</sub>(GAGAGS)<sub>8</sub>] (SEQ ID NO:09), referred to as SELP6.

Example 2. SELP films.

SELP films that were approximately 0.05 mm thickness were produced by solvent evaporation.

Approximately 1.7 grams of each polymer, except for SELP7 where only 1.05 grams was used, were solubilized in 34 mls of 88% formic acid. The solution was stirred for 7 hours at room temperature to insure complete solubilization. The solution was then poured into a film casting apparatus consisting essentially of a rectangular polyethylene trough with a removable polyethylene bottom. The casting apparatus was placed in a vacuum oven attached to a nitrogen gas source for sparging the atmosphere. The films were dried in

the sealed oven drawing a 10-15 micron vacuum with a slow continual influx of nitrogen gas at 60-75° C. After 15-18 hours of drying, the apparatus was disassembled and the film was peeled off the polyethylene bottom. The films were  
5 exposed for 5 minutes to a basic atmosphere (5% open solution of ammonium hydroxide in a sealed desiccator) to neutralize any residual formic acid.

A polyethylene sheet of the same area dimensions as the protein film was roughened by hand using fine grit sand  
10 paper and a fine film of cyanoacrylate glue was spread over its surface. The protein film was applied to the wet surface. A teflon sheet was placed on top and bottom of the polyethylene and protein layers and stainless steel plates were placed around those. The entire assembly was pressed  
15 in a Carver laboratory press at a force of 0.8 metric tons for 18 hours at room temperature. The polyethylene/protein film laminated sheet was placed on a cutting board and 1.3 cm diameter discs were punched out using a stainless steel punch and rubber mallet. The discs were placed individually  
20 in stoppered glass vials.

Specimens were produced from each of the polymers as well as denatured collagen protein (DCP) produced identically as described for the SELP films. Bovine collagen (fibrillar form, lot number 921101) was obtained  
25 from Colla-Tec, Inc. (Plainsboro, New Jersey). It was completely solubilized in 88% formic acid producing a clear but viscous solution. All specimens were sterilized by electron beam irradiation at 2.5 +/- 0.2 Mrads. Each disk was implanted subcutaneously in the back of rats such that  
30 the protein film was in direct contact with the muscle tissue. The specimens remained in the animals for different periods of time: one, four and seven weeks post implantation. At each time interval six specimens per polymer group were retrieved for protein analysis.  
35 Additional specimens from each group were evaluated for tissue reaction by histology.

Non-implanted and retrieved specimens were analyzed to determine the mass of SELP film contained per specimen. Amino acid analysis was performed on each specimen by sealing them individually in an hydrolysis vial with  
5 constant boiling hydrochloric acid and heating for 24 hr at 100-110°C. After hydrolysis, the specimen was extracted and an aliquot of the extract was derivatized with PTC. The derivatized amino acids were separated by reverse phase HPLC and quantified by their absorbance at 254 nm according to  
10 the methods of Henrickson and Meredith (*Anal. Biochem.* 137, 65-74, 1984).

The mass of the SELP film present on each specimen was determined. The amino acid contribution of the SELP protein was estimated based on the total content of the amino acids  
15 G,A,S,V and P which for the pure polymers is >95%. Other amino acids potentially contributed by extraneous protein deposited onto the specimens during residence in the body were excluded from these analyses. Average SELP film mass for non-implanted specimens was determined from the same  
20 batch of specimens used for implantation. Average SELP film mass for retrieved specimens was similarly calculated except that replicates having values greater than two standard deviations from the mean were discarded. Deviations in many cases were due to partial retrieval of specimens that had  
25 fragmented in the tissue after implantation and may not reflect true resorption.

#### Resorption Analysis and Results

Resorption analysis was conducted statistically by  
30 analyzing four specimen population treatment groups. These were: (1) non-implanted; (2) one week post-implantation; (3) four weeks post-implantation; and (4) seven weeks post-implantation.

TABLE 2

Polymer Film Mass Remaining as Determined by AA  
Composition Analysis (in milligrams)

5		SELP0		SELP3		SELP4		SELP5	
	Initial Film Mass	12.21	+/-1.41	5.99	+/-0.46	8.19	+/-0.86	8.51	+/-1.04
	1 Week Film Mass	0.53	+/-0.31	5.93	+/-0.73	7.89	+/-0.55	7.72	+/-1.57
10	4 Week Film Mass	0.27	+/-0.13	6.24	+/-0.61	9.20	+/-1.08	7.49	+/-0.75
	7 Week Film Mass	0.10	+/-0.02	3.49	+/-1.60	8.56	+/-0.67	8.77	+/-0.97
15		SELP7		SELP8		DCP			
	Initial Film Mass	3.27	+/-0.34	8.43	+/-0.59	6.6			+/-1.04
	1 Week Film Mass	4.67	+/-1.33	11.13	+/-1.40	0.15			+/-0.07
20	4 Week Film Mass	0.19	+/-0.16	8.26	+/-1.21	0.09			+/-0.03
	7 Week Film Mass	0.08	+/-0.03	1.52	+/-1.40	0.07			+/-0.03

TABLE 3

25 Polymer Film Remaining as Percent of Non-implanted Mass

		SELP0	SELP3	SELP4	SELP5	SELP7	SELP8	DCP
	Initial ilm Mass	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
30	1 Week Film Mass	4.3%	98.9%	96.3%	90.7%	142.8%	132.0%	2.3%
	4 Week Film Mass	2.2%	104.1%	112.4%	88.0%	5.8%	98.0%	1.3%
35	7 Week Film Mass	0.8%	58.2%	104.5%	103.1%	2.6%	18.1%	1.1%

40 The results from Table 2 are the values for the mass of protein film contained on specimens after implantation. Each value is the mean of at least five specimen masses as determined by amino acid composition. Table 3 displays the same values as a percent of the initial weight prior to

implantation as determined by the mean mass of six specimens of the non-implanted specimens. The results indicate that upon implantation, SELP0 and DCP are substantially resorbed by one week, falling below 5% of their non-implanted masses.

5 SELP7 is substantially resorbed by four weeks with only 5.8% remaining. SELP8 and SELP3 are resorbing by seven weeks with mean values of 18.1% and 58.2% remaining, respectively. SELP4 and SELP5 films show no evidence of resorption at seven weeks.

10 From the above results one may conclude the following. Faster resorption correlates with compositions containing domains of silk-like blocks fewer than eight. The polymers containing eight silk-like blocks have substantially reduced rates of resorption. However, the total content of  
15 silk-like blocks in the copolymer composition does not correlate with resorption rate. While very similar compositionally, SELP7 and SELP8 resorbed quickly, while SELP4 and SELP5 do not resorb in seven weeks. The lack of resorption of SELP4 and SELP5 films at seven weeks  
20 post-implantation corresponds with repeating domains containing greater than eight elastin-like blocks. Although their silk-like block lengths are identical at eight, SELP4 and 5 with elastin-like block lengths of 12 and 16 resorb to a lesser degree than SELP3, which has an elastin-like block  
25 length of 8.

The subject polymers, regardless of their composition, form free-standing films with strength enough to allow easy handling. SELP7 and SELP4 films have tensile strengths of 19+/-1 and 21+/-8 MPa, respectively. The compositional  
30 difference between them that causes SELP7 to resorb in four weeks and SELP4 to remain intact beyond seven weeks makes little apparent difference in their tensile properties. These strengths are adequate for their use in surgical and wound healing applications.

35 The observed resorption of these polymers occurs via surface erosion. This is consistent with the mechanism of degradation of SELP proteins within the body. At



physiological conditions, proteins will degrade only through the action of proteases. Because endogenous proteases are high molecular weight compounds of approximately 20 kDa or greater, their diffusion into the dense SELP films will be limited. The degradation of SELP films is, therefore, progressive from the external surfaces of the material. The subject materials therefore should undergo a slow loss of mechanical integrity while being reduced in mass.

#### 10        Example 2: SELP Porous Sponges

The Function of an implanted material depends greatly on its form, morphology, and mechanical strength, SELP polymers have been fashioned into a variety of forms; dense films, porous sponges, and fibrillar mats. Dense films or sheets, as described above, are semi-permeable barriers which may have utility in surgical repairs by restricting fluid or gas flow, blocking cellular migration, maintaining tissue separations, and confining and protecting implanted organs or devices. Their properties will vary depending on their permeability and their thickness which may range from 0.05 mm to greater than 1 mm. For example varying their thickness will effect their mechanical strength, their resistance to abrasion, and their ultimate resorption.

SELP polymers have been produced as three dimensional, porous sponges to serve as implantable materials that will support cell and tissue ingrowth.

#### Preparation of SELP5 Sponges.

All glassware to come in contact with the protein polymer was depyrogenated by heating to 180°C for 6 hours. SELP5 (0.978 g) was stirred in LAL reagent grade water until dissolved to yield a 1.0% w/v aqueous solution. This solution was aseptically transferred to a 100ml Sr 24/40 pear shaped flask and tared. This flask was fitted with a spray trap, attached to a rotary evaporator, and 65.2 g of water was evaporated using a bath temperature of 39°C, a system pressure of 42 mbar, and a rotation rate of 125 rpm, to yield a solution of 3.0% w/v concentration. This solution

was poured 6mm deep into six standard sterilized Petri dishes (mm diameter); covered with standard lids; placed on a small plastic tray; and placed in a - 8°C freezer overnight. After freezing, the lids were removed from the  
5 Petri dishes; the Petri dishes were placed into a 1200 ml wide mouth lyophilization flask and lyophilized to dryness. After completion of lyophilization, the sponges were removed from their Petri dishes and placed, individually, into a 100ml wide mouth flask containing 75ml of methanol at room  
10 temperature. The head space was evacuated to less than the vapor pressure of the methanol to induce ebullition and insure complete displacement of air entrained within the sponge by the methanol. The sponge, wetted with methanol was allowed to stand for 5 minutes at room temperature at room  
15 temperature. methanol was removed from the sponge by washing 6 times with LAL reagent grade water (175ml per wash) and allowing each was to stand for 5 minutes. The sponges, wetted by water, were returned to 35mm diameter Petri dishes, frozen at -8°C, and again lyophilized. The  
20 lyophilized sponges were placed into new 35mm diameter Petri dishes, lids applied and sealed with parafilm®, placed into a plastic instrument bag, heat sealed, and sterilized using an electron beam irradiation at 2.8 Mrads.

The sponges were dimensionally stable when immersed in  
25 saline or water. When engorged with saline, the sponge turned from white to grey and was somewhat translucent. The engorged sponge retained its original dimensions. Minimal swelling was observed. The geometry and edges of the wet sponge remained unchanged. The observed aqueous stability of  
30 the SELP 5 sponges is different from the properties of collagen hemostatic sponges (Helistat, Marion Laboratories, Kansas City, MO) which almost immediately collapse when exposed to liquid.

SELP5 sponges were cut into 2 x 2 x 0.4 cm specimens and  
35 applied to 2 x2 cm full thickness dermal wounds in pigs. 2 x 2 x 0.3 cm specimens of Helistat were similarly applied to wounds. After bleeding was controlled and the wound flushed

with saline, the specimens were laid into the tissue void such that they would firmly contact the wound bed. The Helistat specimens became completely or partially engorged within a few seconds to several minutes after application  
5 depending on the amount of the blood in the wound. The engorged Helistat specimens collapsed and shrunk resulting in nonuniform coverage of the wound, in some cases, exposing part of the wound beds.

The SELP5 sponges remained substantially white during  
10 the 5 minute observation period after application indicating that they did not immediately absorb blood. One corner of one specimen turned red within a minute after application. It remained physically unchanged. The SELP5 sponges adhered well to the wound bed and could not be lifted out of the  
15 wound with forceps using mild tension. The SELP5 sponges did not shrink upon contact with the bloody tissue and continued to completely cover the wound during observation.

All wounds were covered with petrolatum gauze pads and bandaged. After 7 days, the wounds were undressed and  
20 observed to determine the extent of healing. Wounds containing SELP5 sponges had progressed normally through the healing process as compared to wounds to which no material was applied. The sponge material had not been extruded from the wound as there was no evidence of extraneous material on  
25 the gauze pads. No evidence of excessive inflammation was observed. Epithelialization of the wound was in progress.

### Example 3: SELP Fibrous Meshes

SELP polymers can be fabricated as non-woven fibrous  
30 meshes to produce fibrillar mats which are flexible, have good drapability, and are stable in wet environments. Fibrous meshes with similar physical properties were produced from SELP5, SELP7, and SELPF using the following procedure. 1 gram of polymer was dissolved in 88% formic  
35 acid with stirring at room temperature until homogenous. For SELP5, 5 mls of formic acid were used to dissolve the

lyophilized polymer. For SELP7 and SELPF, 4 and 3 mls of formic acid were used, respectively.

The polymer dope was drawn into a 1cc polypropylene syringe, affixed with a 75mm x 20 gauge stainless steel  
5 hypodermic needle, and mounted on a Sage Instruments syringe pump (model 341B). The pump was set to deliver approximately 0.05 to 0.07 cc/minute. The tip of the needle was placed at 90° to a gas stream delivered from a stainless steel needle (25mm x 20 gauge). A more acute angle was also used. The  
10 dope delivery needle and the gas delivery needle were mounted onto a steel "L"-bracket using miniature "C"-clamps and pads of neoprene rubber such that a gap of 1 mm separated their tips. The tips were displaced in the vertical direction by 0.5 mm such that the gas stream passed  
15 slightly over the flanged end of the hypodermic needle. The gas stream was supplied either with compressed air or high purity (extra dry) nitrogen gas. Compressed air was supplied by an oilless compressor using a diaphragm pump. The air in the reservoir was a ca. 8 atm pressure and was regulated  
20 down to ca. 2-6 atm before being fed to the spray apparatus. When nitrogen was used, it was delivered at 20 psi. The relative humidity was less than 47%.

Fine filaments were formed on and around the edges of a rectangular, 1/16 inch polypropylene mesh that was used as  
25 a target approximately 7-12 inches from needle tips. Filaments streamed off the edges of the target and when they were approximately 5 cm in length, they were collected on a circular, metal wire loop of 38 mm in diameter. Filaments were collected across the loop forming a web of suspended  
30 filaments in the center. The web was removed from the loop by compressing the web between two 35mm polystyrene discs and pressing the web through the wire frame. Fibrous meshes were built up by compressing 5-8 webs between the same discs.

35 The meshes were stabilized by flooding them with 1 ml of either 100% methanol or 100% ethanol and allowing them to dry under ambient conditions. The meshes were sterilized by

electron beam irradiation at a dose of 2.5 MRads. Under microscopic observation, the meshes consisted of fine filaments which varied in diameter from 0.1 to 10 $\mu$ m. The meshes were stable when placed in saline for more than 24  
5 hours.

The meshes were applied to 2 x 2 cm partial and full thickness dermal wounds in pigs in order to investigate their biocompatibility and their ability to incorporate within the healing tissue. The meshes were removed from the  
10 polystyrene discs with forceps and applied to the wound bed. The edges of the meshes could be pulled across the tissue allowing the mesh to be spread and/or rearranged over the wound. The wounds were covered and examined every two days for signs of bioincompatibility. No adverse effects were  
15 observed in wounds containing SELP fibrous meshes. After 14 days, the wounds were completely epithelialized. Histological examination of tissues from wounds to which SELPF fibrous webs had been applied showed that foreign material in the form of filaments had been incorporated into  
20 the healing tissue.

These data indicate that SELP fibrous meshes are well tolerated in healing tissue. Their presence does not interfere with normal healing. In one case, SELP filaments were clearly shown to reside within the healed tissue.

25 SELP films, meshes, and sponges can serve as resorbable packing materials that can be used to augment the loss of soft tissue that occurs during traumatic injury or surgical dissection. Their application at the time of injury can encourage infiltration, overgrowth, and eventual replacement  
30 of the materials with healthy tissue. The mass of the implanted material can provide enough stability to maintain the geometric contours of the body site at which the tissue was lost. Their presence can also mechanically reinforce the wound site such that delicate, healing tissues can form  
35 while protected from further physical injury.

It is evident from the above results, that the subject compositions have particularly desirable properties for uses

in plants. By varying compositional ratios, the rate of resorption can be varied greatly, without significant changes in tensile properties. The compositions can be formed in a wide variety of devices or objects, to find  
5 extensive use for a variety of purposes and context as implants.

All publications and patent applications cited in this specification are herein incorporated by reference as if  
10 each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to  
15 those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- (i) APPLICANT: Protein Polymer Technologies, Inc.
- (ii) TITLE OF INVENTION: Synthetic Proteins As Implantables
- (iii) NUMBER OF SEQUENCES: 9
- (iv) CORRESPONDENCE ADDRESS:
  - (A) ADDRESSEE: Flehr, Hohbach, Test, Albritton & Herbert
  - (B) STREET: Four Embarcadero Center, Suite 3400
  - (C) CITY: San Francisco
  - (D) STATE: CA
  - (E) COUNTRY: U.S.A.
  - (F) ZIP: 94111-4187
- (v) COMPUTER READABLE FORM:
  - (A) MEDIUM TYPE: Floppy disk
  - (B) COMPUTER: IBM PC compatible
  - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
  - (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
- (vi) CURRENT APPLICATION DATA:
  - (A) APPLICATION NUMBER: PCT/US95/
  - (B) FILING DATE:
  - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
  - (A) NAME: Rowland, Bertram I
  - (B) REGISTRATION NUMBER: 20,015
  - (C) REFERENCE/DOCKET NUMBER: FP-58847-1-PC/BIR
- (ix) TELECOMMUNICATION INFORMATION:
  - (A) TELEPHONE: 415-781-1989
  - (B) TELEFAX: 415-398-3249

## (2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 6 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Gly Ala Gly Ala Gly Ser  
1 5

## (2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 5 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Val Pro Gly Val Gly  
1 5

## (2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 936 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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1 5 10 15  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
20 25 30  
 Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala  
35 40 45  
 Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
50 55 60  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
65 70 75 80  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala  
85 90 95  
 Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly  
100 105 110  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
115 120 125  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
130 135 140  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val  
145 150 155 160  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
165 170 175  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
180 185 190  
 Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
195 200 205  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
210 215 220  
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225 230 235 240  
 Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala  
245 250 255  
 Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
260 265 270



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 275 280 285  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala  
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 305 310 315 320  
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 325 330 335  
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 340 345 350  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val  
 355 360 365  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 370 375 380  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 385 390 395 400  
 Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 405 410 415  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 420 425 430  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 435 440 445  
 Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala  
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 Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
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 515 520 525  
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 530 535 540  
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 545 550 555 560  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val  
 565 570 575  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 580 585 590  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 595 600 605  
 Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 610 615 620  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val

-24-

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	660		665		670	
Gly Ala Gly Ser Val Pro Gly Val Gly Val	Pro Gly Val Pro Gly Val Gly Val Pro					
	675		680		685	
Gly Val Gly Val Pro Gly Val Gly Val Pro	Gly Val Gly Val Pro Gly Val Pro Gly					
	690		695		700	
Val Gly Val Pro Gly Val Gly Val Pro Gly	Val Gly Gly Ala Gly Ala					
	705		710		715	
Gly Ser Gly Ala Gly Ala Gly Ser Val Pro	Gly Val Gly Val Pro Gly					
	725		730		735	
Val Gly Val Pro Gly Val Gly Val Pro Gly	Val Gly Val Pro Gly Val Pro Gly Val					
	740		745		750	
Gly Val Pro Gly Val Gly Val Pro Gly Val	Gly Val Pro Gly Val Pro Gly Val Gly					
	755		760		765	
Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala	Gly Ser Val Pro Gly Val					
	770		775		780	
Gly Val Pro Gly Val Gly Val Pro Gly Val	Gly Val Pro Gly Val Pro Gly Val Gly					
	785		790		795	
Val Pro Gly Val Gly Val Pro Gly Val Gly	Val Pro Gly Val Pro Gly Val Gly Val					
	805		810		815	
Pro Gly Val Gly Gly Ala Gly Ala Gly Ser	Gly Ala Gly Ala Gly Ala Gly Ser					
	820		825		830	
Val Pro Gly Val Gly Val Pro Gly Val Gly	Val Pro Gly Val Pro Gly Val Gly Val					
	835		840		845	
Pro Gly Val Gly Val Pro Gly Val Gly Val	Pro Gly Val Pro Gly Val Gly Val Pro					
	850		855		860	
Gly Val Gly Val Pro Gly Val Gly Gly Ala	Gly Ala Gly Ser Gly Ala					
	865		870		875	
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	885		890		895	
Gly Val Gly Val Pro Gly Val Gly Val Pro	Gly Val Gly Val Gly Val Pro Gly					
	900		905		910	
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## (2) INFORMATION FOR SEQ ID NO:4:

- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 832 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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 1 5 10 15  
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 35 40 45  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
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 65 70 75 80  
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 85 90 95  
 Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala  
 100 105 110  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 115 120 125  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 130 135 140  
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 145 150 155 160  
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 165 170 175  
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 195 200 205  
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 210 215 220  
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 225 230 235 240  
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 245 250 255  
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 275 280 285  
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		515					520					525			
Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro
		530					535					540			
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			565					570					575		
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		580					585					590			
Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro
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		660					665					670			
Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
		675					680					685			

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 725 730 735  
 Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala  
 740 745 750  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 755 760 765  
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 770 775 780  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 785 790 795 800  
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 805 810 815  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 820 825 830

## (2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 988 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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 35 40 45  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
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 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val  
 65 70 75 80  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 85 90 95  
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 115 120 125  
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130				135				140							
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145				150						155					160
Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val
			165						170					175	
Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly
			180						185					190	
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
		195					200						205		
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
		210					215				220				
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					230					235					240
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Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
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					310					315					320
Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro
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		370					375				380				
Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly
					390					395					400
Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val
			405						410					415	
Pro	Gly	Val	Gly	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
			420				425						430		
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Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val
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Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly
			485						490					495	

Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
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 515 520 525  
 Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 530 535 540  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
 545 550 555 560  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala  
 565 570 575  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 580 585 590  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 595 600 605  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 610 615 620  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 625 630 635 640  
 Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala  
 645 650 655  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 660 665 670  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val  
 675 680 685  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 690 695 700  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 705 710 715 720  
 Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 725 730 735  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 740 745 750  
 Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly  
 755 760 765  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 770 775 780  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 785 790 795 800  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 805 810 815  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 820 825 830  
 Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 835 840 845  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly

850		855		860
Val Gly Val Pro Gly	Val Gly Val Pro Gly	Val Gly Gly Ala Gly Ala		
865	870	875		880
Gly Ser Gly Ala Gly	Ala Gly Ser Gly Ala Gly	Ala Gly Ser Gly Ala		
	885	890		895
Gly Ala Gly Ser Gly	Ala Gly Ala Gly Ala Gly	Ala Gly Ser		
	900	905		910
Val Pro Gly Val Gly	Val Pro Gly Val Gly	Val Pro Gly Val Gly		
	915	920		925
Pro Gly Val Gly Val	Pro Gly Val Gly Val	Pro Gly Val Gly Val		
	930	935		940
Gly Val Gly Val Pro	Gly Val Gly Gly Ala	Gly Ala Gly Ser Gly		Ala
945	950	955		960
Gly Ala Gly Ser Gly	Ala Gly Ala Gly Ser	Gly Ala Gly Ala Gly		Ser
	965	970		975
Gly Ala Gly Ala Gly	Ser Gly Ala Gly Ala	Gly Ala Gly Ser		
	980	985		

## (2) INFORMATION FOR SEQ ID NO:6:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1056 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Val Pro Gly Val Gly	Val Pro Gly Val Gly	Val Pro Gly Val Gly	Val
1	5	10	15
Pro Gly Val Gly	Val Pro Gly Val Gly	Val Pro Gly Val Gly	Val Pro
	20	25	30
Gly Val Gly Val	Pro Gly Val Gly	Gly Ala Gly Ala	Gly Ser Gly Ala
	35	40	45
Gly Ala Gly Ser	Gly Ala Gly Ser	Gly Ala Gly Ala	Gly Ser
	50	55	60
Gly Ala Gly Ala	Gly Ser Gly Ala	Gly Ala Gly Ser	Gly Ala
	65	70	75
Gly Ser Gly Ala	Gly Ala Gly Ser	Val Pro Gly Val	Gly Val Pro Gly
	85	90	95
Val Gly Val Pro	Gly Val Gly Val	Pro Gly Val Gly	Val Pro Gly
	100	105	110
Gly Val Pro Gly	Val Gly Val Pro	Gly Val Gly Val	Pro Gly Val Gly
	115	120	125
Gly Ala Gly Ala	Gly Ser Gly Ala	Gly Ala Gly Ser	Gly Ala Gly Ala
	130	135	140



Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 145 150 155 160  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 165 170 175  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 180 185 190  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 195 200 205  
 Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala  
 210 215 220  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 225 230 235 240  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 245 250 255  
 Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly  
 260 265 270  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 275 280 285  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 290 295 300  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 305 310 315 320  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 325 330 335  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 340 345 350  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 355 360 365  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 370 375 380  
 Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala  
 385 390 395 400  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 405 410 415  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 420 425 430  
 Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly  
 435 440 445  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 450 455 460  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 465 470 475 480  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 485 490 495  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala

500					505					510					
Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
		515					520					525			
Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val
	530					535					540				
Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro
545					550					555					560
Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
				565					570					575	
Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
			580					585					590		
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
		595						600					605		
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Val	Pro	Gly	Val	Gly	Val	Pro	Gly
	610						615					620			
Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val
625					630					635					640
Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly
				645					650					655	
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
			660					665					670		
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
		675					680					685			
Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
	690					695					700				
Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val
705					710					715					720
Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro
				725					730					735	
Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
			740					745					750		
Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
		755					760					765			
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
	770					775					780				
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Val	Pro	Gly	Val	Gly	Val	Pro	Gly
785					790					795					800
Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val
				805					810					815	
Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly
			820				825					830			
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
		835					840					845			
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
	850					855					860				

Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 865 870 875 880  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 885 890 895  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 900 905 910  
 Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala  
 915 920 925  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 930 935 940  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 945 950 955 960  
 Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly  
 965 970 975  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 980 985 990  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 995 1000 1005  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 1010 1015 1020  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 1025 1030 1035 1040  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 1045 1050 1055

## (2) INFORMATION FOR SEQ ID NO:7:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 972 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 1 5 10 15  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 20 25 30  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
 35 40 45  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala  
 50 55 60  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 65 70 75 80  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser

85								90				95			
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Val	Pro	Gly	Val
			100						105				110		
Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly
		115					120					125			
Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val
	130					135					140				
Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro
145					150					155					160
Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
				165					170					175	
Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
			180						185				190		
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
		195					200					205			
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Val	Pro	Gly	Val	Gly	Val	Pro	Gly
	210					215					220				
Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val
225					230					235					240
Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly
				245						250				255	
Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val
			260				265						270		
Pro	Gly	Val	Gly	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
		275					280					285			
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
	290					295					300				
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
305					310					315					320
Gly	Ala	Gly	Ser	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro
				325						330				335	
Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly
			340				345						350		
Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val
		355					360					365			
Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly
						375					380				
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
385					390					395					400
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
				405						410				415	
Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
			420				425						430		
Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val
		435					440					445			

Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 450 455 460  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
 465 470 475 480  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Gly Ala Gly Ala  
 485 490 495  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 500 505 510  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 515 520 525  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val  
 530 535 540  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 545 550 555 560  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 565 570 575  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 580 585 590  
 Gly Val Gly Val Pro Gly Val Gly Ala Gly Ala Gly Ser Gly Ala  
 595 600 605  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 610 615 620  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 625 630 635 640  
 Gly Ser Gly Ala Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly  
 645 650 655  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 660 665 670  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 675 680 685  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 690 695 700  
 Pro Gly Val Gly Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 705 710 715 720  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 725 730 735  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 740 745 750  
 Gly Ala Gly Ser Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 755 760 765  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
 770 775 780  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 785 790 795 800  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly

805					810					815					
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
			820					825					830		
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
		835					840					845			
Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
		850					855					860			
Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val
		865					870					875			880
Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro
			885					890					895		
Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly
			900					905					910		
Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Gly	Ala	Gly	Ala
		915					920					925			
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
		930					935					940			
Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
		945					950					955			960
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser				
			965					970							

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1024 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val
1				5					10					15	
Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro
		20					25					30			
Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly
		35				40					45				
Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val
	50				55				60						
Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly
65				70				75						80	
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
			85				90						95		
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
		100				105							110		

Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 115 120 125  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 130 135 140  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 145 150 155 160  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
 165 170 175  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 180 185 190  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 195 200 205  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 210 215 220  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 225 230 235 240  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 245 250 255  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 260 265 270  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 275 280 285  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
 290 295 300  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 305 310 315 320  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 325 330 335  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 340 345 350  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 355 360 365  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 370 375 380  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 385 390 395 400  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 405 410 415  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
 420 425 430  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 435 440 445  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 450 455 460  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala

465                      470                      475                      480  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
                                  485                      490                      495  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
                                  500                      505                      510  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
                                  515                      520                      525  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
                                  530                      535                      540  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
                                  545                      550                      555                      560  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
                                  565                      570                      575  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
                                  580                      585                      590  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
                                  595                      600                      605  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
                                  610                      615                      620  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
                                  625                      630                      635                      640  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
                                  645                      650                      655  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
                                  660                      665                      670  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
                                  675                      680                      685  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
                                  690                      695                      700  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
                                  705                      710                      715                      720  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
                                  725                      730                      735  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
                                  740                      745                      750  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
                                  755                      760                      765  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
                                  770                      775                      780  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
                                  785                      790                      795                      800  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
                                  805                      810                      815  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
                                  820                      825                      830



Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 835 840 845  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 850 855 860  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 865 870 875 880  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 885 890 895  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 900 905 910  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 915 920 925  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
 930 935 940  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 945 950 955 960  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 965 970 975  
 Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala  
 980 985 990  
 Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala  
 995 1000 1005  
 Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser Gly Ala Gly Ala Gly Ser  
 1010 1015 1020

## (2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 208 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val  
 1 5 10 15  
 Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro  
 20 25 30  
 Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly  
 35 40 45  
 Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val  
 50 55 60  
 Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly  
 65 70 75 80  
 Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val

85					90					95					
Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro
			100					105					110		
Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly
		115					120					125			
Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val
		130					135					140			
Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly	Val	Pro	Gly	Val	Gly
		145					150					155			160
Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala
				165					170					175	
Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala
			180						185					190	
Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser	Gly	Ala	Gly	Ala	Gly	Ser
		195							200					205	

WHAT IS CLAIMED IS:

1. A protein polymer of at least 15kD and comprising alternating blocks of at least two units each of VPGVG (SEQ ID NO:02) and GAGAGS (SEQ ID NO:01).
2. A protein polymer according to Claim 1, wherein blocks of VPGVG (SEQ ID NO:02) have from two to thirty-two units and blocks of GAGAGS (SEQ ID NO:02) have from two to twelve units.
3. A protein polymer according to Claim 2, wherein said blocks of VPGVG (SEQ ID NO:02) have from eight to twenty units.
4. A protein polymer according to Claim 3, wherein said protein polymer has blocks of VPGVG (SEQ ID NO:02) and GAGAGS (SEQ ID NO:01) with unit ratios of: 8:2; 8:4; 8:6; 12:8; 16:8; and 32:8.
5. A formed object comprising a protein polymer of at least 15kD and comprising alternating blocks of at least two units each of VPGVG (SEQ ID NO:02) and GAGAGS (SEQ ID NO:01).
6. A formed object according to Claim 5, wherein blocks of VPGVG (SEQ ID NO:02) have from two to thirty-two units and blocks of GAGAGS (SEQ ID NO:02) have from two to twelve units.
7. An amorphous mass comprising a protein polymer of at least 15kD and comprising alternating blocks of at least two units each of VPGVG (SEQ ID NO:02) and GAGAGS (SEQ ID NO:01).

8. An amorphous mass according to Claim 7, wherein blocks of VPGVG (SEQ ID NO:02) have from two to thirty-two units and blocks of GAGAGS (SEQ ID NO:01) have from two to twelve units.

9. A film comprising a protein polymer of at least 15kD and comprising alternating blocks of at least two units each of VPGVG (SEQ ID NO:02) and GAGAGS (SEQ ID NO:01).

10. A film according to Claim 9, wherein blocks of VPGVG (SEQ ID NO:02) have from two to thirty-two units and blocks of GAGAGS (SEQ ID NO:01) have from two to twelve units.

11. A sterilized implantable device comprising a protein polymer of at least 15kD and comprising alternating blocks of at least two units each of VPGVG (SEQ ID NO:02) and GAGAGS (SEQ ID NO:01) or a homopolymer of repetitive units of GAGAGS (SEQ ID NO:01).

12. A sterilized implantable device according to Claim 11, wherein blocks of VPGVG (SEQ ID NO:02) have from two to thirty-two units and blocks of GAGAGS (SEQ ID NO:01) have from two to twelve units.

13. A method for maintaining separated viable tissue together, said method comprising:

uniting said separated tissue with a device for holding said tissue together, said device comprising a composition according to Claim 1 or a homopolymer of repetitive units of GAGAGS (SEQ ID NO:01).

14. A method according to Claim 13, wherein said device is a suture, pin, thread, gel, or film.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/02772

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/330, 345, 353, 354, 356, 402, 409; 435/68.1, 320.1; 428/218,220; 602/50; 604/368; 623/1, 11, 66; 930/10, 21, 60

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,215,200 (MIYATA ET AL) 29 July 1980, see entire document	1-14
A	US, A, 4,589,882 (URRY ET AL) 20 May 1986, see entire document.	1-14
X	US, A, 5,243,038 (FERRARI ET AL) 07 September 1993, see in particular Example 4.	1-4
Y		5-14
X	US, A, 5,171,505 (LOCK) 15 December 1992, see sequences.	1-4
Y		5-14



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"A" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

08 JUNE 1995

Date of mailing of the international search report

30 JUN 1995

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# INTERNATIONAL SEARCH REPORT

International application No.

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## A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

C12N 15/11, 15/62; C07K 14/00, 14/195, 17/00; C08L 89/06; A61F 2/02, 2/06; A61K 38/00, 38/02, 38/16, 38/39; C09H 1/00; D01F 4/00

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

530/330, 345, 353, 354, 356, 402, 409; 435/68.1, 320.1; 428/218,220; 602/50; 604/368; 623/1, 11, 66; 930/10, 21, 60